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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,861	03/05/2001	James R. Broach	60623CIP(50370)	4402

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PETER C. LAURO
EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,861	BROACH ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61 and 109-119* is/are pending in the application.

4a) Of the above claim(s) *4-43,45-50,52,55,58,61 and 109-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,44,51,53,54,56,57,59 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/12/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-61 and 109-119 are presently pending.

Claims 1 and 2 (in part); 3, 44, 51, 53, 54, 56, 57, 59 and 60 are under consideration.

Claims 4-43, 45-50, 52, 55, 58, 61 and 109-119 are withdrawn from consideration as being directed to a nonelected invention.

Election/Restrictions

Applicant's election with traverse of Group 3 (claims 1 and 2 (in part); 3 and 44-61) drawn to:

recombinant yeast comprising heterologous GPCR and chimera of GPA1 ($\geq$ 4 c-terminal substituted with heterologous G protein subunit amino acids) and optionally linked to at least the 1st five amino acids of a 2nd heterologous G protein subunit.

In the reply filed on 8/20/04 is acknowledged. The traversal is on the ground(s) that neither King nor Kang contain a specific disclosure of any of the four members of the Markush of Claim 1; nor do the references disclose "the ability of the claimed chimeric G protein subunits to functionally couple to the heterologous receptor and activate the pheromone pathway". This argument is not found persuasive for the reasons provided in the previous action. The presently claimed invention does not share a common special technical feature since recombinant yeast cells comprising fusions between heterologous G-Protein coupled receptors (GPCR) and chimeric G protein subunits (e.g yeast/mammals) are known in the art. See e.g. King et al. US Pat. No. 5,482,835 and Kang (1990 Mol. Cell. Biol. 10:2582-2590) cited in the specification. Additionally, chimeras within the scope of the presently claimed invention which are incorporated in

yeast with coupled heterologous receptors which activate the pheromone pathway is known in the art and as such cannot constitute a "special" technical feature. See. Pausch et al. WO 95/21925 (8/95), Fowlkes et al. WO 94/23025(10/94: filed 3/94 or earlier), Brown et al. WO 99/14344, and Conklin et al. Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890 discussed in prior art rejections below. See also MPEP Annex B: Unity of Invention Part 1: Instructions Concerning Unity of Invention: use of a *posteriori* evidence of lack of unity. Still further, the Office action pointed out additional uncontroverted evidence of lack of unity e.g. lack of core structure among the various Markush members of claim 1.

Applicant further argues that "a sufficient search and examination with respect to the subject matter of all claims can be made without serious burden" (citing MPEP 803).

This argument was considered but deemed nonpersuasive for the following reasons. The necessity of a burdensome search requirement applies to U.S. practice and not PCT lack of unity. In any event, the lack of common (e.g. core) structure present among the members of the Markush group and the methods (e.g. of Groups 4 and 5) being drawn to different method objectives, which utilize diverse reagents and reaction conditions is sufficient to justify a burdensome search.

Applicant's election of the *"single disclosed species"* of the human bradykinin receptor as the heterologous G protein coupled receptor and the sandwich chimera Galphaq(1-11)-GPA1 (6-467)-Galpaq(355-359) of Example 12, which substitutes both the N and C terminus of GPA1 with 1st and 2nd heterologous subunits derived from the same source, in the reply filed on 8/20/04 is acknowledged. Because applicant did not

distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is noted that applicant failed to indicate the claims readable on the "single disclosed species". Accordingly, the elected species apparently reads on claims 1 and 2 (in part); 3, 44, 51, 53, 54, 56, 57, 59 and 60.

Claims 45-50, 52, 55, 58 and 61 (which do not read on the elected species due to different substitution criteria e.g. don't *substitute* both N and C terminus of GPA1 and/or containing additional components e.g. "a heterologous polypeptides"; a "reporter construct"; gene mutations etc. not contained within the elected species) are withdrawn from consideration as being directed to a nonelected invention.

The requirement is still deemed proper and is therefore made FINAL.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The present application (09/581,861 filed 3/5/2001) claims priority under:

a. 371 of PCT/US98/21168 (filed 10/07/98); and

b. CIP of 08/946,298 (filed 10/7/97) as well as earlier applications.

Upon review of the two above cited documents, the presently claimed (and elected invention) finds disclosure support in the PCT/US98/21168 application (filed 10/07/98) BUT not the 08/946,298 (filed 10/7/97) application which lacks direct or exemplary support for the presently claimed scope of claims e.g. the substitution GPA variants as well as the sandwich chimeras. Accordingly, the present elected claims are granted the filing date of the PCT application (e.g. 10/7/98) for purposes of prior art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 44 and 56, are rejected under 35 U.S.C. 102(a,b,e) as being anticipated by Pausch et al. WO 95/21925 (8/95).

Pausch et al. teach "chimeric G-Protein subunits" comprising a chimeric G-protein subunit comprising GPA1 in which "at least the last 4" C-terminal amino acids are substituted by " at least the last 4 C-terminal amino acids of a heterologous G protein subunit; and recombinant yeast cell" comprising:

A. a heterologous G-protein coupled receptor (GPCR) which acts as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell ; and

B. the above "chimeric G-Protein subunits" such that expression of the chimeric G-protein subunit functionally integrates said heterologous GPCR into the pheromone response pathway of the yeast cell and wherein modulation of the signal transduction activity of the heterologous GPCR by an extracellular signal provides a detectable signal. E.g. see Pausch et al. Abstract; pages 3-5; pages 13-14 (especially page 14,

lines 1-20 and particularly lines 5-10 and lines 17-20); pages 19-24; examples and claims 1-29.

The Pausch et al. teaching (e.g. page 14, lines 1-20 and particularly lines 5-10 and lines 17-20) that in a "particularly preferred embodiment" that the "carboxyl terminal domain" of GPA1 can be substituted by the carboxyl terminal domain of a heterologous Galpha is within the scope of "at least 4 C-terminal amino acids" since this encompasses the entire C-terminus.

Claims 1-2, 44 and 56, are rejected under 35 U.S.C. 102(a,b,e) as being anticipated by Fowlkes et al. WO 94/23025(10/94: filed 3/94 or earlier).

Fowlkes et al. teach "chimeric G-Protein subunits" comprising a chimeric G-protein subunit comprising the yeast G alpha unit (e.g. GPA1) in which at least 10, 20 or 40 (only final 10 or 20 deemed critical: see page 43-top of page 44) of the yeast's C-terminal amino acids are substituted by with a substantially homologous mammalian (or other exogenous) C-terminal amino acids G alpha; and recombinant yeast cell" comprising:

A. a heterologous G-protein coupled receptor (GPCR) which acts as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell ; and

B. the above "chimeric G-Protein subunits" such that expression of the chimeric G-protein subunit functionally integrates said heterologous GPCR into the pheromone response pathway of the yeast cell and wherein modulation of the signal transduction

activity of the heterologous GPCR by an extracellular signal provides a detectable signal. E.g. see Fowlkes et al. Abstract; pages 7-9; pages 12-17; page 23-25; pages 37-40 ; pages 43-44, particularly bottom of page 43-top of page 44 ; examples and claims 1-37 (especially for example claims 1, 28 and 29).

The Fowlkes teaching of yeast comprising alpha chimeras composed of N-terminal yeast alpha subunits fused to at least 10, 20 or 40 C-terminal yeast amino acids is within the scope of "at least 4 C-terminal amino acids" as presently claimed.

Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Brown et al. WO 99/14344.

Brown et al. teach "chimeric G-Protein subunits" comprising GPA1 in which "a minimum of at least three amino acids within the C-terminal ten" are substituted by the corresponding C-terminal amino acids of a heterologous G protein subunit with five (5) amino acids being preferred (e.g. see abstract; pages 5-7; examples and claims); and recombinant yeast cell" comprising:

A. a heterologous G-protein coupled receptor (GPCR) which acts as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell ; and

B. the above "chimeric G-Protein subunits" such that expression of the chimeric G-protein subunit functionally integrates said heterologous GPCR into the pheromone response pathway of the yeast cell and wherein modulation of the signal transduction

activity of the heterologous GPCR by an extracellular signal provides a detectable signal. The Brown et al. teaching of 3-10 and particularly 5 C-terminal GPA1 substitutions anticipates the presently claimed invention with the lower limit of four (4) (or 5 which is anticipated by the reference example) substitutions being immediately envisaged (e.g. anticipated) or alternatively prima facie obvious to one of ordinary skill in the art due to the limited Markush of 3-10 and the exemplified embodiment of five substitutions.

Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al. and Conklin et al. Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890.

Pausch et al. teach "chimeric G-Protein subunits" comprising a chimeric G-protein subunit comprising GPA1 in which "at least the last 4" C-terminal amino acids are substituted by " at least the last 4 C-terminal amino acids of a heterologous G protein subunit; and recombinant yeast cell" comprising:

A. a heterologous G-protein coupled receptor (GPCR) which acts as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell ; and

B. the above "chimeric G-Protein subunits" such that expression of the chimeric G-protein subunit functionally integrates said heterologous GPCR into the pheromone response pathway of the yeast cell and wherein modulation of the signal transduction activity of the heterologous GPCR by an extracellular signal provides a detectable

signal. E.g. see Pausch et al. Abstract; pages 3-5; pages 13-14 (especially page 14, lines 1-20 and particularly lines 5-10 and lines 17-20); pages 19-24; examples and claims 1-29.

The Pausch et al. teaching (e.g. page 14, lines 1-20 and particularly lines 5-10 and lines 17-20) that in a "particularly preferred embodiment" that the "carboxyl terminal domain" of GPA1 can be substituted by the carboxyl terminal domain of a heterologous Galpha is within the scope of "at least 4 C-terminal amino acids" since this encompasses the entire C-terminus.

The Pausch et al. reference differs from the presently claimed invention by failing to teach substituting the lower limit of C-terminal amino acids (e.g. four amino acids) of GPA1 or substitution of the last five (5) C-terminal GPA1 amino acids (e.g. claim 57).

However, the Pausch reference teaches that:

a. the "carboxyl terminal domain" of GPA1 can be substituted by the carboxyl terminal domain of a heterologous Galpha; and

b. that "One can easily determine which configuration is best suited for adequate coupling to a particular heterologous receptor by simply constructing vectors as taught herein and measuring the signaling of ligand binding in response to a given assay"

See Pausch at page 14.

Accordingly, it would be obvious to one of ordinary skill in the art at the time of applicant's invention to determine optimum minimum C-terminal GPA1 length necessary to obtain coupling as well as additional amino acids encompassing such a minimum number (e.g. 5, 6 ... entire C-terminus) for a particular heterologous receptor.

Alternatively, in this regard, the Conklin reference provides evidence that substitution of "at least four C-terminal" Galpha amino acids are necessary (e.g. both –3 and –4 positions) in order to permit coupling to a new (e.g. heterologous receptor). See e.g. abstract and data obtained therein.

Thus, in light of the Conklin reference teaching, the selection of "at least four C-terminal GPA1 amino acids" or 5 or more up to the entire C-terminus, for substitution with the corresponding C-terminal heterologous Galpha would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to obtrain coupling to a particular heterologous receptor.

Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fowlkes et al. WO 94/23025(10/94: filed 3/94 or earlier).

Fowlkes et al. teach "chimeric G-Protein subunits" comprising a chimeric G-protein subunit comprising the yeast G alpha unit (e.g. GPA1) in which at least 10, 20 or 40 (only final 10 or 20 deemed critical: see page 43-top of page 44) of the yeast's C-terminal amino acids are substituted by with a substantially homologous mammalian (or other exogenous) C-terminal amino acids G alpha; and recombinant yeast cell" comprising:

A. a heterologous G-protein coupled receptor (GPCR) which acts as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell ; and

B. the above "chimeric G-Protein subunits" such that expression of the chimeric G-protein subunit functionally integrates said heterologous GPCR into the pheromone response pathway of the yeast cell and wherein modulation of the signal transduction activity of the heterologous GPCR by an extracellular signal provides a detectable signal. E.g. see Fowlkes et al. Abstract; pages 7-9; pages 12-17; page 23-25; pages 37-40 ; pages 43-44, particularly bottom of page 43-top of page 44 ; examples and claims 1-37 (especially for example claims 1, 28 and 29).

The Fowlkes teaching of yeast comprising alpha chimeras composed of N-terminal yeast alpha subunits fused to at least 10, 20 or 40 C-terminal yeast amino acids is within the scope of "at least 4 C-terminal amino acids" as presently claimed.

The Fowlkes et al. reference differs from the presently claimed invention by failing to teach substituting the lower limit of C-terminal substitution (e.g. four amino acids) of GPA1 or substitution of the last five (5) C-terminal GPA1 amino acids (e.g. claim 57).

However, in this regard, the Conklin reference provides evidence that substitution of "at least four C-terminal" Galpha amino acids are necessary (e.g. both –3 and –4 positions) in order to permit coupling to a new (e.g. heterologous receptor). See e.g. abstract and data obtained therein.

Thus, in light of the Conklin reference teaching, the selection of "at least four C-terminal GPA1 amino acids" or 5 or more up to the entire C-terminus, for substitution with the corresponding C-terminal heterologous Galpha would have been obvious to

one of ordinary skill in the art at the time of applicant's invention in order to obtain coupling to a particular heterologous receptor.

Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. WO 99/14344 and Conklin et al. Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890.

Brown et al. teach "chimeric G-Protein subunits" comprising a chimeric G-protein subunit comprising GPA1 in which "a minimum of at least three within the C-terminal ten" are substituted by the corresponding C-terminal amino acids of a heterologous G protein subunit with five (5) amino acids being preferred (e.g. see abstract; pages 5-7; examples and claims); and "recombinant yeast cell" comprising:

A. a heterologous G-protein coupled receptor (GPCR) which acts as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell ; and

B. the above "chimeric G-Protein subunits" such that expression of the chimeric G-protein subunit functionally integrates said heterologous GPCR into the pheromone response pathway of the yeast cell and wherein modulation of the signal transduction activity of the heterologous GPCR by an extracellular signal provides a detectable signal. The Brown et al. teaching of 3-10 and particularly C-terminal GPA1 substitutions anticipates the presently claimed invention with the lover limit of four (4) substitituions being immediately envisaged (e.g. anticipated) or alternatively prima facie

obvious to one of ordinary skill in the art due to the limited Markush of 3-10 and the exemplified embodiment of five substitutions

The Brown et al. reference differs, if at all, from the presently claimed invention by failing to *explicitly* teach substituting the lower limit of C-terminal amino acids(e.g. four amino acids) of GPA1 or substitution of the last five (5) C-terminal GPA1 amino acids (e.g. claim 57).

However, in view of the Brown teaching of the Markush of 3-10, substitutions and its preferred examples teaching five, it would be obvious to one of ordinary skill in the art at the time of applicant's invention to determine optimum minimum C-terminal GPA1 length necessary to obtain coupling as well as additional amino acids encompassing such a minimum number (e.g. 5, 6 ... entire C-terminus) for a particular heterologous receptor.

Alternatively, in this regard, the Conklin reference provides evidence that substitution of "at least four C-terminal" Galpha amino acids are necessary (e.g. both –3 and –4 positions) in order to permit coupling to a new (e.g. heterologous receptor). See e.g. abstract and data obtained therein.

Thus, further in light of the Conklin reference teaching, the selection of "at least four C-terminal GPA1 amino acids" or 5 or more up to the entire C-terminus, for substitution with the corresponding C-terminal heterologous Galpha would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to obtain coupling to a particular heterologous receptor.

Claims 1-3, 44, 51, 53, 54, 56, 57, 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al. WO 95/21925 (8/95), Fowlkes et al. WO 94/23025(10/94: filed 3/94 or earlier), Brown et al. WO 99/14344, and Conklin et al. Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890 as applied to claims 1-2, 44, 56 and 57 above, and further in view of Hamm, J. Biol. Chem. Vol. 273(2) (Jan. 1998) pages 669-672.

The teaching of the Pausch et al., Fowlkes et al. and Brown et al. references taken separately or in combination with the Conklin reference, as discussed in the above rejections, is hereby incorporated by reference in their entirety. As discussed above, the above references teach recombinant yeast cells comprising heterologous G-protein coupled receptor (GPCR) which act as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell ; and "chimeric G-Protein subunits" such that expression of the chimeric G-protein subunit comprising a GPA1 subunit C-terminally substituted with at least the last four C-terminal amino acids of a heterologous G alpha protein subunit functionally integrates said heterologous GPCR into the pheromone response pathway of the yeast cell, wherein modulation of the signal transduction activity of said heterologous GPCR by an extracellular signal provides a detectable signal.

The above reference teaching of a chimeric Galpha protein subunit differs from the presently claimed invention (e.g. claims 1-2{in part}, claim 3, 51,53, 54, 59 and 60) by failing to additionally modify the N-terminus portion of GPA1 to operably link "at least

the first five N-terminal amino acids (e.g. the 1st 11 N-terminal amino acids: see claims 54 and 60) of a 2nd heterologous G protein subunit.

The Hamm reference teaches the structure and role of the G protein heterotrimer; particularly the different Galpha subunits and their corresponding receptors (e.g. including bradykinin: see page 669; page 670, right column). The Hamm reference teaches that in addition to the C-terminus of G protein alpha subunits being critical in determining receptor-G protein specificity (as discussed in the above Pausch, Fowlkes, Brown and Conklin references), the N-terminus of the alpha G-protein subunit also appears to be involved in promoting heterologous receptor contact or coupling. E.g. see Abstract; page 669, especially right column; the figures, especially figures 1 and 2, but particularly figure 2 and the role of the 1st N-terminal 23 amino acids of Galpha and rhodopsin receptor)

Accordingly, the Hamm reference would provide motivation to one of ordinary skill in the art at the time of applicant's invention to further modify the chimeric Galpha protein subunits obtained by the Pausch, Fowlkes, Brown and Conklin references by linking or substituting into the N terminal portion of the reference chimeras corresponding heterologous amino acids in order to obtain sandwich chimeras (e.g. N-term heterologous-GPA1-C terminal heterologous) that can be screened for different degrees (e.g. increased/decreased) of heterologous receptor coupling.

The determination of the optimum number of N-terminally linked or substituted heterologous amino acids (e.g. at least 5 ; i.e. 11) with regard to a particular heterologous receptor and corresponding chimera construct was well within the skill of

the art utilized art-recognized screening techniques. E.g. see Pausch, Fowlkes, Brown and Conklin references and assays disclosed therein.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to additionally modify the N-terminus portion of GPA1 of the Pausch, Fowlkes, Brown and Conklin references chimeras to operably link "at least the first five N-terminal amino acids (e.g. the 1st 11 N-terminal amino acids: see claims 54 and 60) of a heterologous G protein subunit and arrive at the presently claimed sandwich chimeras with a reasonable expectation of success of obtaining modified chimeras which possessed varying degrees (e.g. increased/decreased) of heterologous receptor coupling for use in screening assays (e.g. receptor agonists/antagonists).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

October 14, 2004